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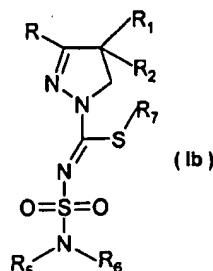
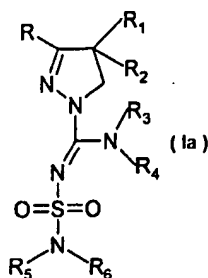
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(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING POTENT CB1-ANTAGONISTIC ACTIVITY



(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives which are potent cannabinoid (CB<sub>1</sub>) receptor antagonists with utility for the treatment of diseases connected with disorders of the cannabinoid system. The compounds have the general formula (Ia) or (Ib) wherein the symbols have the meanings given in the specification. The invention also relates to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

#### 4,5-Dihydro-1H-pyrazole derivatives having potent CB<sub>1</sub>-antagonistic activity

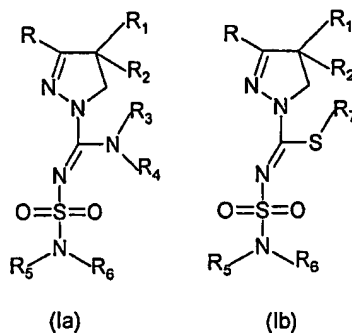
5 The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned 4,5-dihydro-1H-pyrazoles are potent cannabinoid (CB<sub>1</sub>) receptor antagonists with utility for the treatment of disorders involving cannabinoid neurotransmission.

10

Cannabinoids are present in the Indian hemp *Cannabis sativa* and have been used as medicinal agents for centuries (Mechoulam, R. and Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, 24, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of cannabinoid receptors (CB<sub>1</sub> and CB<sub>2</sub>) stimulated the search for novel cannabinoid receptor antagonists (Munro, S. *et al.*, *Nature* **1993**, 365, 61. Matsuda, L.A. and Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system (Consroe, P. *Neurobiology of Disease* **1998**, 5, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, 1, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, 12, 458. Pertwee, R.G., *Progress in Neurobiology* **2001**, 63, 569). Hitherto, several CB<sub>1</sub> receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB<sub>1</sub> receptor antagonists. A representative example is SR-141716A (Dutta, A.K. *et al.*, *Med. Chem. Res.* **1994**, 5, 54. Lan, R. *et al.*, *J. Med. Chem.* **1999**, 42, 769. Nakamura-Palacios, E.M. *et al.*, *CNS Drug Rev.* **1999**, 5, 43). CP-272871 is a pyrazole derivative, like SR141716A, but less potent and less CB<sub>1</sub> receptor subtype-selective than SR141716A (Meschler, J.P. *et al.*, *Biochem. Pharmacol.* **2000**, 60, 1315). Aminoalkylindoles have been disclosed as CB<sub>1</sub> receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in 1995. AM-630 is a moderately active CB<sub>1</sub> receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K. *et al.*, *Life Sc.* **1997**, 61, PL115). Researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB<sub>1</sub> receptor antagonists (e.g. LY-320135) (Felder, C.C. *et al.*, *J. Pharmacol. Exp. Ther.* **1998**, 284, 291). 3-Alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M. *et al.*, *Biorg. Med.Chem. Lett.* **1999**, 9, 2233). Aventis Pharma claimed diarylmethyleneazetidine analogs as CB<sub>1</sub> receptor antagonists (Mignani, S. *et al.*, Patent FR 2783246, 2000; *Chem. Abstr.* **2000**, 132, 236982). Tricyclic pyrazoles were claimed by Sanofi-Synthelabo as CB<sub>1</sub> antagonists (Barth, F. *et al.*, Patent WO 0132663, 2001; *Chem. Abstr.* **2001**, 134, 340504). Interestingly, many CB<sub>1</sub> receptor

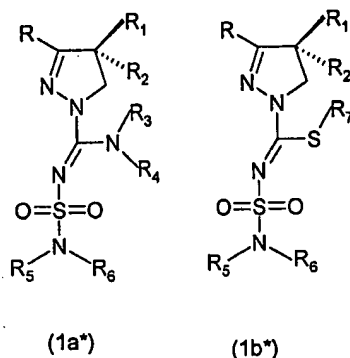
- antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S. *et al.*, *Eur. J. Pharmacol.* **1997**, 334, R1). Reviews provide a nice overview of the cannabinoid research area (Mechoulam, R. *et al.*, *Prog. Med. Chem.* **1998**, 35, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, 6, 635. Mechoulam, R. *et al.*, *Eur. J. Pharmacol.* **1998**, 359, 1. Williamson, E.M. and Evans, F.J. *Drugs* **2000**, 60, 1303.
- 5 Pertwee, R.G. *Addiction Biology* **2000**, 5, 37. Robson, P. *Br. J. Psychiatry* **2001**, 178, 107. Pertwee, R. G. *Prog. Neurobiol.* **2001**, 63, 569. Goya, P and Jagerovic, N. *Exp. Opin. Ther. Patents* **2000**, 10, 1529. Pertwee, R. G. *Gut* **2001**, 48, 859).
- 10 It has now surprisingly been found that potent and selective antagonism of cannabinoid-CB<sub>1</sub> receptors is present in the novel 4,5-dihydro-1H-pyrazole derivatives of the formula (Ia) or (Ib), prodrugs thereof, tautomers thereof and salts thereof



- 15 where in
- R and R<sub>1</sub> independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from
  - 20 the group C<sub>1-3</sub>-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C<sub>1-2</sub>)-amino, mono- or dialkyl (C<sub>1-2</sub>)-amido, (C<sub>1-3</sub>)-alkyl sulfonyl, dimethylsulfamido, C<sub>1-3</sub>-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R<sub>1</sub> represent naphthyl,
  - 25 – R<sub>2</sub> represents hydrogen, hydroxy, C<sub>1-3</sub>-alkoxy, acetyloxy or propionyloxy,
  - R<sub>3</sub> represents a hydrogen atom or a branched or unbranched C<sub>1-8</sub> alkyl group or a C<sub>3-7</sub> cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
  - R<sub>4</sub> represents a hydrogen atom or a branched or unbranched C<sub>1-8</sub> alkyl,
  - 30 C<sub>3-8</sub> cycloalkyl, C<sub>2-10</sub> heteroalkyl, C<sub>3-8</sub> nonaromatic heterocycloalkyl or C<sub>4-10</sub> nonaromatic heterocycloalkyl-alkyl moiety which moieties may contain one or more heteroatoms from the group (O, N, S), which moieties may be substituted with a keto group, trifluoromethyl group, C<sub>1-3</sub> alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R<sub>4</sub> represents an
  - 35 amino, hydroxy, phenoxy or benzyloxy group or R<sub>4</sub> represents a branched or

- unbranched C<sub>1-8</sub> alkoxy, C<sub>3-8</sub> alkenyl, C<sub>5-8</sub> cycloalkenyl or C<sub>6-9</sub> cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or -SO<sub>2</sub>- group which C<sub>1-8</sub> alkoxy, C<sub>3-8</sub> alkenyl, C<sub>5-8</sub> cycloalkenyl or C<sub>6-9</sub> cycloalkenylalkyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R<sub>4</sub> represents a phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings may be substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above, or
- R<sub>4</sub> represents a group NR<sub>8</sub>R<sub>9</sub> with the proviso that R<sub>3</sub> represents a hydrogen atom or a methyl group and wherein R<sub>8</sub> and R<sub>9</sub> are the same or different and represent C<sub>1-4</sub> alkyl or C<sub>2-4</sub> trifluoroalkyl or R<sub>8</sub> and R<sub>9</sub> - together with the nitrogen atom to which they are bonded - form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or -SO<sub>2</sub>- group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a C<sub>1-4</sub> alkyl group or
- R<sub>3</sub> and R<sub>4</sub> - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or -SO<sub>2</sub>- group, which moiety may be substituted with a C<sub>1-4</sub> alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidiny, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group,
- R<sub>5</sub> and R<sub>6</sub> independently of each other represent a hydrogen atom or a branched or unbranched C<sub>1-8</sub> alkyl or alkenyl group which groups may contain one or more heteroatoms from the group (O, N, S), a keto group or a -SO<sub>2</sub>- group and which groups may be substituted with a hydroxy or amino group, or R<sub>5</sub> and R<sub>6</sub> independently of each other represent a C<sub>3-8</sub> cycloalkyl group or C<sub>3-8</sub> cycloalkenyl group which may contain one or more ring heteroatoms from the group (O, N, S) or the -SO<sub>2</sub>- group and which groups may be substituted with a hydroxy group, alkyl (C<sub>1-3</sub>), the -SO<sub>2</sub>- group, the keto group, amino group, monoalkylamino group (C<sub>1-3</sub>) or dialkylamino group (C<sub>1-3</sub>), or
- R<sub>5</sub> represents a naphthyl group or a phenyl group which phenyl group may be substituted with 1, 2 or 3 substituents Y wherein Y has the meaning as described hereinabove, with the proviso that R<sub>6</sub> represents a hydrogen atom, or a branched or unbranched alkyl group (C<sub>1-5</sub>) which alkyl group may contain one or more heteroatoms from the group (O, N, S) or the -SO<sub>2</sub>- group and which alkyl group may be substituted with a hydroxy, keto or amino group, or
- R<sub>5</sub> and R<sub>6</sub> - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group which may contain ring heteroatoms from the group (O, N, S), the keto or the SO<sub>2</sub> group and which

- monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with a hydroxy group, alkyl (C<sub>1-3</sub>) group, SO<sub>2</sub> group, keto group, amino group, monoalkylamino group (C<sub>1-3</sub>), dialkylamino group (C<sub>1-3</sub>), pyrrolidinyl group or piperidinyl group, which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y, wherein Y has the meaning as described herein above,
- R<sub>7</sub> represents branched or unbranched C<sub>1-3</sub> alkyl.
- At least one centre of chirality is present (at the C<sub>4</sub> position of the 4,5-dihydro-1H-pyrazole moiety) in the compounds of the formula (Ia) and (Ib). The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (Ia) or (Ib). Particular compounds of interest of formula (Ia) or (Ib) have the absolute stereoconfiguration at the C<sub>4</sub> position of the 4,5-dihydro-1H-pyrazole moiety as represented by the formulas (1a\*) and (1b\*):



The invention also relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (Ia) or (Ib).

20

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

25

Due to the potent CB<sub>1</sub> antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetite, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelination related disorders, as well as for the treatment of pain disorders,

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including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

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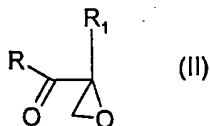
The affinity of the compounds of the invention for cannabinoid CB<sub>1</sub> receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB<sub>1</sub> receptor is stably transfected in conjunction with [3H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

15 The cannabinoid CB<sub>1</sub> antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB<sub>1</sub> receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB<sub>1</sub> receptors by CB<sub>1</sub> receptor agonists (e.g. CP-55,940 or (R)-WIN-20 55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB<sub>1</sub> receptor-mediated response can be antagonised by CB<sub>1</sub> receptor antagonists such as the compounds of the invention.

Intermediates having formula (II) (see below) can be obtained according to methods known, for example: a) Francotte, E.; Tong, Z. *Chem. Abstr.* **126**, 213598; b) Rempfler, H. and Kunz, W. *Chem. Abstr.* **113**, 40432; c) Rempfler, H. and Kunz, W. *Chem. Abstr.* **107**, 217473.

Intermediates having formula (III) wherein R<sub>2</sub> represents hydrogen (see below) can be obtained according to methods known, for example: a) EP 0021506; b) DE 30 2529689, c) Grosscurt, A.C. et al., *J. Agric. Food Chem.* **1979**, 27, (2), 406.

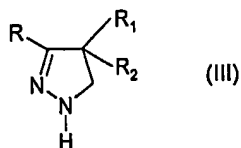
Intermediates having formula (III) wherein R<sub>2</sub> represents a hydroxy group can be obtained by reacting a compound having formula (II) with hydrazine or hydrazine hydrate



35

This reaction, preferably carried out in an organic solvent such as ethanol, yields a compound having formula (III) wherein R<sub>2</sub> represents a hydroxy group.

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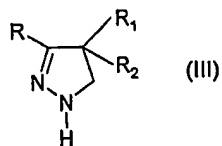


Suitable synthetic routes for the compounds of the invention are the following:

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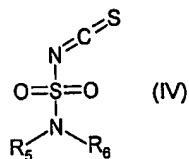
### Synthetic route A

Step 1: reaction of a compound having formula (III)

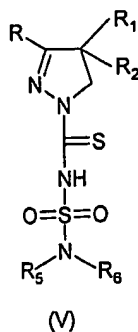


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with a compound having formula (IV).



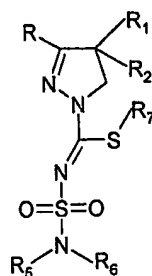
- 15 This reaction is preferably carried out in an organic solvent, such as for example dichloromethane, and yields a compound having formula (V) wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub> and R<sub>6</sub> have the meaning as described above for compound (Ia), and which are new.



20

Step 2: reaction of a compound having formula (V) with a compound R<sub>7</sub>-X, wherein X represents a leaving group, for example an iodide group, and R<sub>7</sub> has the meaning as described above for (Ib) gives a compound having formula (Ib).

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(lb)

This reaction is preferably carried out in the presence of a base, for example triethylamine.

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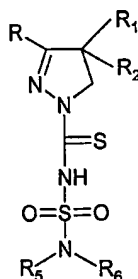
Step 3: reaction of a compound having formula (lb) with an amine having formula  $\text{HNR}_3\text{R}_4$  wherein  $\text{R}_3$  and  $\text{R}_4$  have the meanings as described above, analogous to the method described in *Synth. Commun.* **1996**, 26, (23), 4299.

This reaction gives a compound having formula (la).

10

#### Synthetic route A1

Step 1: Reaction of a compound having formula (V)



(V)

15

with an amine having formula  $\text{HNR}_3\text{R}_4$  wherein  $\text{R}_3$  and  $\text{R}_4$  have the meanings as described above in the presence of a mercury(II) salt, for example  $\text{HgCl}_2$ , gives a compound having formula (la).

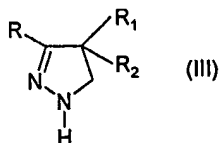
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This reaction is preferably carried out in an organic solvent, such as for example acetonitrile, analogous to the method described in *Synth. Commun.* **1996**, 26, (23), 4299.



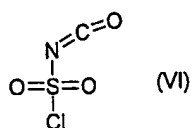
**Synthetic route A2**

Step 1: reaction of a compound having formula (III)



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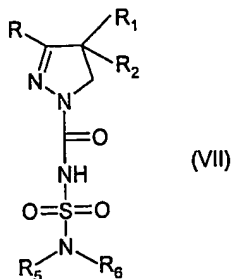
with a isocyanate derivative having formula (VI), followed by treatment with an amine  $\text{HNR}_5\text{R}_6$



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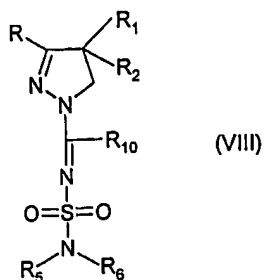
This reaction is preferably carried out in an organic solvent like dichloromethane, and yields a compound having formula (VII). Compounds having formula (VII) wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub> and R<sub>6</sub> have the meaning as described herein above for compound (Ia) are new.

15



Step 2: reaction of a compound having formula (VII) with a halogenating agent, such as for example  $\text{PCl}_5$ , gives a compound having formula (VIII)

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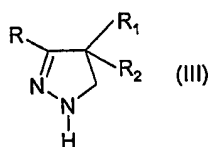
wherein  $R_{10}$  represents a halogen atom, for example a chloro atom. This reaction is preferably carried out in an organic solvent such as chlorobenzene.

Compounds having formula (VIII) wherein  $R$ ,  $R_1$ ,  $R_2$ ,  $R_5$  and  $R_6$  have the meanings as described above for compound (Ia) and wherein  $R_{10}$  represents a halogen atom, are new.

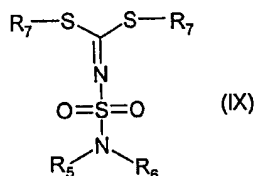
Step 3: reaction, preferably carried out in an inert organic solvent such as dichloromethane, of a compound having formula (VIII) with an amine having formula  $HNR_3R_4$  wherein  $R_3$  and  $R_4$  have the meanings as described above gives a compound having formula (Ia).

### Synthetic route A3

Step 1: reaction of a compound having formula (III)



with a compound having formula (IX)



gives a compound having formula (Ib), (see e.g. *Chem. Ber.* **1966**, 99, 2885 and *Chem. Ztg.* **1984**, 108, (12), 404).

The preparation of the compounds is illustrated in the following examples.

#### Example 1

**3-(4-Chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine**

Part A: To a stirred solution of ((ethyl)propylamino)sulfonyl isothiocyanate (5.98 gram, 25.4 mmol) in dry dichloromethane in a nitrogen atmosphere is added of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (6.52 gram, 25.4 mmol). After stirring for 90 minutes the resulting solution is concentrated *in vacuo* and purified by column chromatography ( $CH_2Cl_2$ , silicagel,  $R_f \sim 0.45$ ). The resulting solid is recrystallized from diethyl ether to give 3-(4-chlorophenyl)-N-

(((ethyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (6.57 gram, 56 % yield). Melting point: 144-146 °C.

Part B: To a stirred suspension of 3-(4-chlorophenyl)-N-(((ethyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (2.32 gram, 5 mmol) in acetonitrile (20 mL) is added cold methylamine (4 mL). To the resulting solution is added a solution of HgCl<sub>2</sub> (1.5 gram) in acetonitrile (10 mL). The resulting black suspension is stirred for four hours. The precipitate is removed by filtration. The filtrate is concentrated *in vacuo*, dissolved in dichloromethane and successively washed with aqueous 0.5 N NaOH solution and water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting oil is crystallized from diethyl ether to give 3-(4-chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (1.78 gram, 77 % yield). Melting point (MP): 129-131 °C.

In an analogous manner the compounds having formula (Ia) listed below have been prepared:

2. 3-(4-Chlorophenyl)-N'-(((ethyl)methylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 112-115 °C.
3. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-hydroxyethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 104-106 °C.
4. 3-(4-Chlorophenyl)-N-(2-hydroxyethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI<sup>+</sup>): 490 (MH<sup>+</sup>).
5. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-(morpholin-4-yl)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI<sup>+</sup>): 547 (MH<sup>+</sup>).
6. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-(morpholin-4-yl)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
7. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-(dimethylamino)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI<sup>+</sup>): 505 (MH<sup>+</sup>).
8. 3-(4-Chlorophenyl)-N-(3-(dimethylamino)propyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
9. 3-(4-Chlorophenyl)-N-(2-(piperidin-1-yl)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI<sup>+</sup>): 557 (MH<sup>+</sup>).
10. 3-(4-Chlorophenyl)-N-(2-(morpholin-4-yl)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI<sup>+</sup>): 559 (MH<sup>+</sup>); MP: 174-176 °C.
11. 3-(4-Chlorophenyl)-N-(2-(dimethylamino)ethyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
12. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
13. 3-(4-Chlorophenyl)-N-(3-(dimethylamino)propyl)-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI<sup>+</sup>): 519 (MH<sup>+</sup>).

14. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide hemifumarate. MP: 182-185 °C.
15. 3-(4-Chlorophenyl)-N-(2-(dimethylamino)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. Amorphous.
- 5 16. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. Amorphous.
17. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(1-methylpiperidin-4-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. Amorphous.
18. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-hydroxyethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 123-126 °C.
- 10 19. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. Amorphous.  $R_f \sim 0.4$  (diethyl ether).
20. 3-(4-Chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-Methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 129-131 °C.
- 15 21. 3-(4-Chlorophenyl)-N-methyl-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. Amorphous.  $R_f \sim 0.3$  (MTBE).
22. 3-(4-Chlorophenyl)-N-methyl-N'-(((methyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 132-134 °C.
23. 3-(4-Chlorophenyl)-N,N-dimethyl-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. Amorphous.  $R_f \sim 0.25$  (MTBE).
- 20 24. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 175-177 °C.
25. 3-(4-Chlorophenyl)-N'-((hexahydro-1H-azepin-1-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. Amorphous.
- 25 26. 3-(4-Chlorophenyl)-N'-((dipropylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 141-142 °C.
27. 3-(4-Chlorophenyl)-N'-(((isopropyl)methylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 134-136 °C.
28. 3-(4-Chlorophenyl)-N-methyl-N'-((octahydroazocin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 165-168 °C.
- 30 29. 3-(4-Chlorophenyl)-N-ethyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. Amorphous.
30. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide. MP: 166-168 °C.

35

**Example 31****3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-propyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide**

**Part A:** To a stirred solution of chlorosulfonyl isocyanate (1.73 mL, 20 mmol) in dry dichloromethane (20 mL) is very slowly added a solution of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (5.13 gram, 20 mmol) in dry dichloromethane (125 mL) at - 5 °C. After stirring for 30 minutes the reaction mixture is allowed to attain

40

room temperature and stirred for another 2 hours. After cooling to 0 °C liquid dimethylamine (5 mL) is added and the resulting solution is stirred for another hour at 0 °C and for 2 hours at room temperature. The solution is washed with water, filtered over hyflo and concentrated *in vacuo*. Flash chromatography (MTBE,  $R_f \sim 0.3$ ) gives  
5 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (4.75 g, 58 %). MP: 210-212 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1.47 gram, 3.62 mmol) and phosphorus pentachloride (0.80 gram, 3.84 mmol) in chlorobenzene (20 mL) is heated at reflux  
10 temperature for 1 hour. After thorough concentration *in vacuo*, the formed 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidoyl chloride is suspended in dry dichloromethane and reacted with cold *n*-propylamine (1.0 mL) at 0 °C. After stirring for 1 hour, the mixture is dissolved in ethyl acetate and washed with water and concentrated *in vacuo*. The residue is purified by  
15 column chromatography (dichloromethane/acetone = 19/1 (v/v),  $R_f \sim 0.35$ ) to give an oil (0.82 g). Crystallisation from diethyl ether, followed by recrystallisation from ethanol gives 3-(4-chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-propyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (0.38 gram, 23 % yield). MP: 127-129°C.

20 In an analogous manner the compounds having formula (Ia) listed below have been prepared:

32. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-fluoroethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 128-131 °C.  
25 33. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-N-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 158-159 °C.  
34. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 170-172 °C.

30 Example 35

**3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester**

Part A: To a stirred solution of (piperidin-1-yl)sulfonyl isothiocyanate (54.77 g, 266 mmol) in dry dichloromethane (900 mL) in a nitrogen atmosphere is added 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (68.3 gram, 266 mmol). After stirring  
35 for 16 hours an additional amount of dichloromethane is added. The resulting solution is twice washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated *in vacuo*. After addition of MTBE, the residue crystallizes. The crystalline material is collected and washed with MTBE to give 3-(4-chlorophenyl)-4-phenyl-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (77.6 gram, 63 % yield).  
40

Part B: To a stirred solution of 3-(4-chlorophenyl)-4-phenyl-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (30 gram, 64.9 mmol) in acetone (1 L) is added triethylamine (18.0 mL, 130 mmol). To the resulting yellow solution is added methyl iodide (9.12 g, 64 mmol) and the resulting solution is stirred

for 16 hours at room temperature. The formed precipitate is removed by filtration. The filtrate is washed with water, concentrated *in vacuo* to give a yellow solid. Recrystallisation from MTBE gives 3-(4-chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (27.9 gram, 90% yield). MP: 192-194 °C.

In an analogous manner the compounds having formula (Ib) listed below have been prepared:

- 10 36. 3-(4-Chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 159-160 °C.
37. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 141-143 °C.
38. 3-(4-Chlorophenyl)-4-phenyl-N-((1,2,3,4-tetrahydroisoquinolin-2-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 143-145 °C.
- 15 39. 3-(4-Chlorophenyl)-N-(((ethyl)phenylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 143-146 °C.
40. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
- 20 41. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
42. 3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
43. 3-(4-Chlorophenyl)-N-((dimethylamino)sulfonyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
- 25 44. 3-(4-Chlorophenyl)-N-(((ethyl)methylamino)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 133-136 °C.
45. 3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 182-185 °C.
- 30 46. 3-(4-Chlorophenyl)-N-((morpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 202-204 °C.
47. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 205-207 °C.
48. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 196-198 °C.
- 35 49. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((dimethylamino)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 181-183 °C.
50. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 231-233 °C.
- 40 51. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 221-225 °C.

52. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((dimethylamino)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 181-185°C.
53. 3-(4-Chlorophenyl)-N-((1,1-dioxidothiomorpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 216-217 °C.
- 5 54. 3-(5-Chlorothien-2-yl)-N-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.

Example 55**3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine**

- 5 To a cooled mixture (< 0 °C) of 3-(4-chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidioic acid methyl ester (10.0 gram, 21 mmol) in methanol (75 mL) is added cold methylamine (15 mL). The resulting mixture is allowed to attain room temperature and stirred for 3 hours at 50 °C. After cooling to room temperature the mixture is concentrated *in vacuo*, dissolved in  
10 dichloromethane, washed twice with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Subsequent flash chromatography (EtOAc/MeOH/NH<sub>4</sub>OH (25 % aq.) = 95/5/0.5 (v/v)), followed by recrystallisation from diisopropyl ether gives 3-(4-chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine (7.87 gram, 81 % yield) as a white solid. MP: 175-177 °C.

15

In an analogous manner the compounds having formula (Ia) listed below - including those in table 1 - have been prepared:

- 5 56. 3-(4-Chlorophenyl)-N-cyclopropyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 142-144 °C.  
20 57. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 180-182 °C.  
58. 3-(5-Chlorothien-2-yl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 122-123 °C.  
25 59. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 169-170 °C.  
60. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(1-methylpiperidin-4-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 144-146 °C.  
30 61. 3-(4-Chlorophenyl)-N-cyclopropyl-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 150-151 °C.  
62. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-ethyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 116-119 °C.  
63. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N,N-dimethyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 135-137 °C.  
35 64. N'-((Diethylamino)sulfonyl)-N,N-dimethyl-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 159-160 °C.  
65. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 81-85 °C.  
40 66. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-ethyl,N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.  
67. 3-(4-Chlorophenyl)-N-ethyl,N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 178 °C.  
68. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-ethyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 162-165 °C.  
45 69. 3-(4-Chlorophenyl)-N-methyl-N'-((1,2,3,4-tetrahydroisoquinolin-2-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.  
70. 3-(4-Chlorophenyl)-N'-((ethylphenylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 145-147 °C.



71. N'-((Diethylamino)sulfonyl)-3-(4-chlorophenyl)-N-methyl-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 109-111 °C.
72. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 157-159 °C.
- 5 73. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 85-89 °C.
74. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 178-182 °C.
- 10 75. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 168-170 °C.
76. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 65-68 °C.
77. 3-(4-Chlorophenyl)-N'-(((ethyl)methylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 125-128 °C.
- 15 78. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 174-177 °C.
79. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 223-235 °C.
- 20 80. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 214-216 °C.
81. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 260-263 °C.
82. 3-(4-Chlorophenyl)-4-(3-fluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 170 °C.
- 25 83. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 223-225 °C.
84. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-(2-fluorophenyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 173-175 °C.
85. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-(3-fluorophenyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 110 °C.
- 30 86. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 165-168 °C.
87. 3-(4-Chlorophenyl)-N'-((1,1-dioxidothiomorpholin-4-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 268-271 °C.
- 35 88. 3-(4-Chlorophenyl)-N'-((4-hydroxypiperidin-1-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 80 °C.

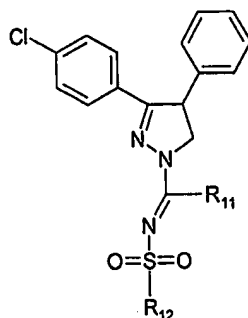


Table 1

Example:	R <sub>11</sub>	R <sub>12</sub>	MP (°C)	Salt form
89:	4-Methyl-1,4-diazepan-1-yl	Dimethylamino	197-200	0.5 Fumarate
90:	1,4-Diazepan-1-yl	Piperidin-1-yl	Amorphous	
91:	1,4-Diazepan-1-yl	Dimethylamino	Amorphous	
92:	4-Methyl-1,4-diazepan-1-yl	Piperidin-1-yl	159-164	

93:	4-Methylpiperazin-1-yl	Dimethylamino	191-193	
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Example 94

5 **3-(4-Chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester**

**Part A:** A stirred mixture of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (3.21 gram, 11.3 mmol), [(4-methylpiperazin-1-yl)sulfonyl]dithioimido- carbonic acid dimethyl ester (3.08 gram, 12.0 mmol) and pyridine (25 mL) is heated at 100 °C for  
 10 24 hours in a nitrogen atmosphere. After cooling to room temperature the mixture is concentrated *in vacuo*, water is added and the resulting mixture is extracted with dichloromethane. The dichloromethane extract is washed twice with water, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Subsequent flash chromatographic purification gives 3-(4-chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-4-phenyl-  
 15 4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (4.24 gram, 76 % yield) as an amorphous solid. (*R<sub>f</sub>* ~ 0.1, EtOAc/methanol = 95/5 (v/v)).

In an analogous manner the compounds having formula (Ib) listed below have been prepared:

20

95. 3-(4-Chlorophenyl)-N-(((2-(dimethylamino)ethyl)ethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester.  
 MP: 158 °C.

25 96. N-((Diethylamino)sulfonyl)-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.  
*R<sub>f</sub>* ~ 0.4 (MTBE).

97. 3-(4-Chlorophenyl)-N-([(1,4']bipiperidin-1'-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 245 °C.

30 98. 3-(4-Chlorophenyl)-N-(((1-methylpiperidin-4-yl)methylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Oil. *R<sub>f</sub>* ~ 0.15 (methanol/dichloromethane = 5/95 (v/v)).

99. 3-(4-Chlorophenyl)-N-((4-methyl-1,4-diazepan-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.  
*R<sub>f</sub>* ~ 0.10 (methanol/dichloromethane = 5/95 (v/v)).

35

Example 100

**(-)-(4S)-3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine**

40 (-)-(4S)-3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine (3.8 gram, 8.3 mol) ( $[\alpha]^{25}_D = -139^\circ$ , *c* = 0.006, MeOH) was obtained as an amorphous solid via chiral chromatographic separation of racemic 3-(4-chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-

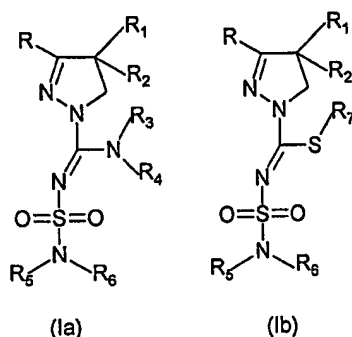
dihydro-1H-pyrazole-1-carboxamidine (7.87 gram, 17.1 mmol) using a chiral stationary phase Chiralpak AD. The mobile phase consisted of methanol/diethylamine = 999/1 (v/v).

- 5 In an analogous manner the optically pure compounds listed below have been prepared from the corresponding racemates:

101. (-)-(4S)-3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralcel OD). Mobile phase consisted of hexane/2-propanol = 80/20 (v/v). ( $[\alpha]^{25}_D$ ) = -147 °, c = 0.01, MeOH). Amorphous.
- 5 102. (-)-(4S)-3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of methanol/diethylamine = 999/1 (v/v). ( $[\alpha]^{25}_D$ ) = -171 °, c = 0.005, MeOH). Amorphous.
- 10 103. (-)-(4S)-3-(4-Chlorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. ( $[\alpha]^{25}_D$ ) = -144 °, c = 0.01, MeOH). (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of ethanol. Amorphous.

**Claims**

## 1. Compounds of the general formulas (Ia) or (Ib)



5

wherein

- R and R<sub>1</sub> independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group C<sub>1-3</sub>-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C<sub>1-2</sub>)-amino, mono- or dialkyl (C<sub>1-2</sub>)-amido, (C<sub>1-3</sub>)-alkyl sulfonyl, dimethylsulfamido, C<sub>1-3</sub>-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R<sub>1</sub> represent naphthyl,
- R<sub>2</sub> represents hydrogen, hydroxy, C<sub>1-3</sub>-alkoxy, acetyloxy or propionyloxy,
- R<sub>3</sub> represents a hydrogen atom or a branched or unbranched C<sub>1-8</sub> alkyl group or a C<sub>3-7</sub> cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
- R<sub>4</sub> represents a hydrogen atom or a branched or unbranched C<sub>1-8</sub> alkyl, C<sub>3-8</sub> cycloalkyl, C<sub>2-10</sub> heteroalkyl, C<sub>3-8</sub> nonaromatic heterocycloalkyl or C<sub>4-10</sub> nonaromatic heterocycloalkyl-alkyl moiety which moieties may contain one or more heteroatoms from the group (O, N, S), which moieties may be substituted with a keto group, trifluoromethyl group, C<sub>1-3</sub> alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R<sub>4</sub> represents an amino, hydroxy, phenoxy or benzyloxy group or R<sub>4</sub> represents a branched or unbranched C<sub>1-8</sub> alkoxy, C<sub>3-8</sub> alkenyl, C<sub>5-8</sub> cycloalkenyl or C<sub>6-9</sub> cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or -SO<sub>2</sub>- group which C<sub>1-8</sub> alkoxy, C<sub>3-8</sub> alkenyl, C<sub>5-8</sub> cycloalkenyl or C<sub>6-9</sub> cycloalkenylalkyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R<sub>4</sub> represents a phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings may be substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above, or

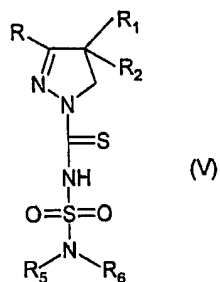
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- $R_4$  represents a group  $NR_8R_9$  with the proviso that  $R_3$  represents a hydrogen atom or a methyl group and wherein  $R_8$  and  $R_9$  are the same or different and represent  $C_{1-4}$  alkyl or  $C_{2-4}$  trifluoroalkyl or  $R_8$  and  $R_9$  - together with the nitrogen atom to which they are bonded - form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or  $-SO_2-$  group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a  $C_{1-4}$  alkyl group or
- $R_3$  and  $R_4$  - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or  $-SO_2-$  group, which moiety may be substituted with a  $C_{1-4}$  alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidiny, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group,
- $R_5$  and  $R_6$  independently of each other represent a hydrogen atom or a branched or unbranched  $C_{1-8}$  alkyl or alkenyl group which groups may contain one or more heteroatoms from the group (O, N, S), a keto group or a  $-SO_2-$  group and which groups may be substituted with a hydroxy or amino group, or  $R_5$  and  $R_6$  independently of each other represent a  $C_{3-8}$  cycloalkyl group or  $C_{3-8}$  cycloalkenyl group which may contain one or more ring heteroatoms from the group (O, N, S) or the  $-SO_2-$  group and which groups may be substituted with a hydroxy group, alkyl ( $C_{1-3}$ ), the  $-SO_2-$  group, the keto group, amino group, monoalkylamino group ( $C_{1-3}$ ) or dialkylamino group ( $C_{1-3}$ ), or
- $R_5$  represents a naphthyl group or a phenyl group which phenyl group may be substituted with 1, 2 or 3 substituents Y wherein Y has the meaning as described hereinabove, with the proviso that  $R_6$  represents a hydrogen atom, or a branched or unbranched alkyl group ( $C_{1-5}$ ) which alkyl group may contain one or more heteroatoms from the group (O, N, S) or the  $-SO_2-$  group and which alkyl group may be substituted with a hydroxy, keto or amino group, or
- $R_5$  and  $R_6$  - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group which may contain ring heteroatoms from the group (O, N, S), the keto or the  $SO_2$  group and which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with a hydroxy group, alkyl ( $C_{1-3}$ ) group,  $SO_2$  group, keto group, amino group, monoalkylamino group ( $C_{1-3}$ ), dialkylamino group ( $C_{1-3}$ ), pyrrolidinyl group or piperidinyl group, which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y, wherein Y has the meaning as described herein above,
- $R_7$  represents branched or unbranched  $C_{1-3}$  alkyl.

and tautomers, stereoisomers, prodrugs and salts thereof.

2. Pharmaceutical compositions containing a pharmacologically active amount of at least one compound as claimed in claim 1 as an active component.
- 5 3. Method of preparing pharmaceutical compositions as claimed in claim 2 characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.
- 10 4. Process for the preparation of compounds having formula (Ib), characterized in that a compound is prepared wherein R, R<sub>1-2</sub>, R<sub>5</sub>-R<sub>6</sub> and R<sub>7</sub> have the meanings given in claim 1 by
  - 15 1) reacting a compound having formula (III) with a compound having formula (IV) to give a compound of the formula (V) which is reacted with a compound of the formula R<sub>7</sub>-X, or
  - 20 2) reacting a compound having formula (III) with a compound having formula (IX).
5. Process for the preparation of compounds having formula (Ia), characterized in that a compound is prepared wherein R and R<sub>1</sub>-R<sub>6</sub> have the meanings given in claim 1 by
  - 25 1) reacting a compound having formula (Ib), with an amine of the formula HNR<sub>3</sub>R<sub>4</sub>, or
  - 2) reacting a compound having formula (V) with an amine of the formula HNR<sub>3</sub>R<sub>4</sub> in the presence of a mercury (II) salt, or
  - 30 3) reacting a compound having formula (III) with a compound of the formula (VI) to give a compound of the formula (VII) which is reacted with a halogenating agent to give a compound of the formula (VIII) which is reacted with an amine of the formula HNR<sub>3</sub>R<sub>4</sub>.
- 35 6. Compounds of the general formula (V)

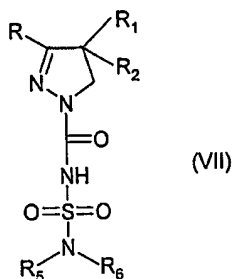
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wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub> and R<sub>6</sub> have the meanings given in claim 1.

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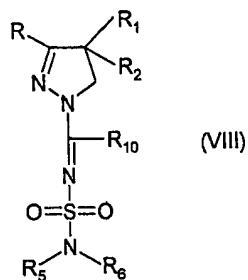
7. Compounds of the general formula (VII)



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wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub> and R<sub>6</sub> have the meanings given in claim 1.

8. Compounds of the general formula (VIII)



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wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>5</sub> and R<sub>6</sub> have the meanings given in claim 1 and wherein R<sub>10</sub> represents a halogen atom.

20

9. Use of a compound as claimed in claim 1 for the preparation of a pharmaceutical composition for the treatment of disorders involving cannabinoid neurotransmission.



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/10435

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 7 A61K31/415 C07D231/06 C07D401/12 A61K31/4155 A61K31/4725  
 C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 01 70700 A (SOLVAY PHARMACEUTICALS B V) 27 September 2001 (2001-09-27) see the formula (i) definition for Aa, and formulae IX, VII and X (claims 8-10) ---	1-10
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A	US 4 070 365 A (VAN DAALLEN JAN JOHANNES ET AL) 24 January 1978 (1978-01-24) the whole document --- -/--	1-10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*A\* document member of the same patent family

Date of the actual completion of the international search

22 November 2002

Date of mailing of the international search report

29/11/2002

Name and mailing address of the ISA

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 Fax (+31-70) 340-3016

Authorized officer

Scruton-Evans, I

10. Use as claimed in claim 9 characterised in that said disorders are psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetite, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelination related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	<p>WO 00 46209 A (SANOFI SYNTHELABO ;BARTH FRANCIS (FR); CAMUS PHILIPPE (FR); MARTIN)            10 August 2000 (2000-08-10)            the whole document</p> <p>-----</p>	1-10

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Information on patent family members

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